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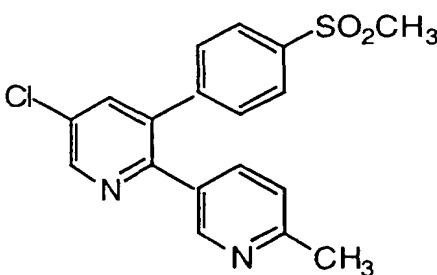
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(54) Title: 5-CHLORO-3-(4-METHANESULFONYLPHENYL)-6'-METHYL-[2,3']BIPYRIDINYL IN PURE CRYSTALLINE FORM AND PROCESS FOR SYNTHESIS



(A)

(57) Abstract: This invention encompasses a pharmaceutical composition comprising the compound of formula A: A in combination with a pharmaceutically acceptable carrier, said compound being comprised of about 1-50%, 1-20% or 1-10% of the polymorphic form which is designated Form V and the remainder of the compound being comprised of at least one polymorphic form selected from the group consisting of: Form I, Form II, Form III and Form IV

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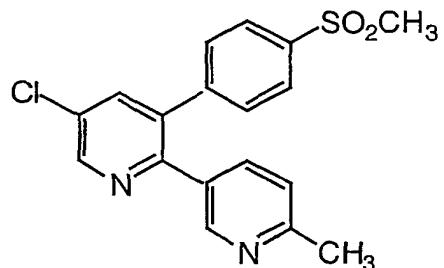
5-CHLORO-3-(4-METHANESULFONYLPHENYL)-6'-METHYL-[2,3']BIPYRIDINYL IN PURE CRYSTALLINE FORM AND PROCESS FOR SYNTHESIS

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BACKGROUND OF THE INVENTION

The present invention relates to the Form V polymorph of Compound A having the chemical structure shown below:

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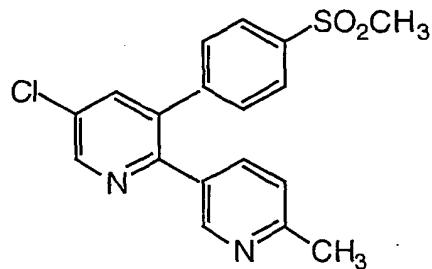
Compound A

as well as a process for synthesizing the Form V polymorph.

Compound A exists in five polymorphic forms (Forms I-V), an amorphous form and two hydrated forms. The compound is a potent and selective cyclooxygenase-2 (COX-2) inhibitor, useful primarily in the treatment of inflammation, pain and fever as well as other COX-2 mediated diseases, such as described in PCT Publication Nos. WO96/10012 and WO96/16934. Compound A is described in U.S. Patent No. 5,861,419 granted on January 19, 1999 (Example 23), which is hereby incorporated by reference in its entirety. A process for making Compound A is described in U.S. Patent No. 6,040,319 granted on March 21, 2000, which is hereby incorporated by reference in its entirety. The present invention unexpectedly provides for a novel, robust process for making a Form V polymorph of compound A from any one of Forms I, II, III or IV or any mixture of polymorphs of compound A.

SUMMARY OF THE INVENTION

This invention encompasses the Form V polymorph of structural
5 formula A:



A

which is useful in the treatment of cyclooxygenase-2 mediated diseases.

10 The invention encompasses certain pharmaceutical compositions for
the treatment of cyclooxygenase-2 mediated diseases comprising the Form V
polymorph of Compound A. The invention also encompasses a process for
synthesizing the Form V polymorph of Compound A comprising: combining
polymorph I, II, III or IV of Compound A with isopropyl acetate; heating to an
15 elevated temperature less than about 75°C; and cooling to a low temperature to
produce the Form V polymorph.

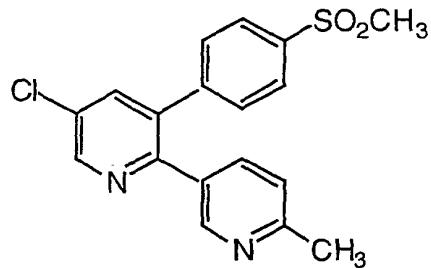
BRIEF DESCRIPTION OF THE DRAWINGS

The invention is described in connection with the appended drawings
20 in which:

Fig. 1 is the X-ray powder diffraction (XRPD) pattern of Form V;
Fig. 2 is the XRPD pattern of Form I;
Fig. 3 is the XRPD pattern of Form II;
Fig. 4 is the XRPD pattern of Form III;
25 Fig. 5 is the XRPD pattern of Form IV;
Fig. 6 is the XRPD pattern of the hemihydrate; and
Fig. 7 is the XRPD pattern of the sesquihydrate.

DETAILED DESCRIPTION

This invention encompasses the Form V polymorph of structural formula A:



5

A

having the following physical characteristics: DSC extrapolated onset melting temperature of 133.9°C, DSC peak melting temperature of 134.5°C, and x-ray powder diffraction peak positions, Cu K alpha, of: 13.7, 7.2, 6.9, 6.7, 5.8, 5.7, 5.0, 4.9, 4.8, 4.7, 4.5, 4.2, 4.0, 3.9, 3.8, 3.7, 3.6, 3.4, 3.3, 3.1, 3.0, 2.9 and 2.8 angstroms.

10

An embodiment of the invention is the Form V polymorph of Compound A characterized as having an x-ray powder diffraction pattern peak position, Cu K alpha, at about 13.7 angstroms. Within this embodiment of the invention is the Form V polymorph of Compound A further characterized as having at least one x-ray powder diffraction pattern peak position, Cu K alpha, at about: 7.2, 6.9, 6.7, 5.8, 5.7, 5.0, 4.9, 4.8, 4.7, 4.5, 4.2, 4.0, 3.9, 3.8, 3.7, 3.6, 3.4, 3.3, 3.1, 3.0, 2.9 or 2.8 angstroms.

15

An embodiment of the invention is the Form V polymorph of Compound A characterized as having a DSC extrapolated onset melting temperature of about 133.9°C.

20

An embodiment of the invention is the Form V polymorph of Compound A characterized as having a DSC peak melting temperature of about 134.5°C.

An embodiment of the invention is the Form V polymorph of Compound A having the aforesaid characteristics in substantially pure form.

25

The invention also encompasses a pharmaceutical composition comprising a non-toxic therapeutically effective amount of a Form V polymorph of Compound A and a pharmaceutically acceptable carrier.

An embodiment of the invention encompasses a method of treating an

inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent comprising administering to a patient in need of such treatment a non-toxic therapeutically effective amount of a Form V polymorph of Compound A.

- Another embodiment of the invention encompasses a method of
5 treating a cyclooxygenase mediated disease advantageously treated by an active agent that selectively inhibits cyclooxygenase-2 in preference to cyclooxygenase-1 comprising administering to a patient in need of such treatment a non-toxic therapeutically effective amount of a Form V polymorph of Compound A.

- Another embodiment of the invention encompasses a method for
10 treating an illness selected from the group consisting of: (a) rheumatic fever, (b) symptoms associated with influenza or other viral infections, common cold, (c) low back and neck pain, (d) dysmenorrhea, (e) headache, (f) toothache, (g) sprains and strains, (h) myositis, (i) neuralgia, (j) synovitis, (k) arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis,
15 (l) bursitis, (m) burns, (n) injuries, and (o) following surgical and dental procedures, comprising administering to a patient in need of such treatment a non-toxic therapeutically effective amount of a Form V polymorph of Compound A.

This invention also encompasses a novel process for making a Form V polymorph of structural formula A comprising: combining polymorph I, II, III or IV of
20 Compound A with isopropyl acetate; heating to an elevated temperature less than about 75°C; and cooling to a low temperature to produce the Form V polymorph.

For purposes of this Specification, the term 'elevated temperature' means any temperature above room temperature but less than about 75°C, as high as about 35-70°C, preferably about 50-65°C. Room temperature is about 20°C. The
25 term 'low temperature' means any temperature below the 'elevated temperature', as low as about 0-30°C, preferably as low as about 10-20°C.

Polymorphic forms of Compound A, for purposes of this invention, are identified as Form I (onset of melting m.p. $135.7 \pm 0.2^\circ\text{C}$, peak m.p. $137.0 \pm 0.2^\circ\text{C}$),
Form II (onset of melting m.p. 129.6°C , peak m.p. 131.5°C), Form III (onset of
30 melting m.p. 133.2°C , peak m.p. 134.4°C), Form IV (onset of melting m.p. $133.72 \pm 0.04^\circ\text{C}$, peak m.p. $134.5 \pm 0.1^\circ\text{C}$) and Form V (onset of melting, m.p. 133.9°C , peak m.p. 134.5°C). Forms I through V are anhydrous.

An embodiment of the invention encompasses the process for making the Form V polymorph of Compound A which further comprises isolating the Form V

polymorph. A subset of this embodiment encompasses isolating the Form V polymorph by filtration.

An embodiment of the invention is the process for making a Form V polymorph of Compound A wherein the elevated temperature is about 40-75°C.

- 5 Another embodiment of the invention is the process for making a Form V polymorph of Compound A wherein the elevated temperature is about 50-65°C.

An embodiment of the invention is the process for making a Form V polymorph of Compound A wherein the low temperature is about 0-30°C. Another embodiment of the invention is the process for making a Form V polymorph of
10 Compound A wherein the low temperature is about 10-20°C.

Another embodiment of the invention is the process for making a Form V polymorph of Compound A wherein the elevated temperature is about 50-65°C and the low temperature is about 10-20°C.

- The invention will now be illustrated by the following non-limiting
15 examples:

PREPARATIVE EXAMPLE A

The starting material Compound A was made in accordance with U. S. Pat. No. 6,040,319.

20

PREPARATIVE EXAMPLE B

FORM II

- Form II was obtained by crystallizing Compound A obtained in accordance with Preparative Example A from ethyl acetate. Differential Scanning
25 Calorimetry showed an extrapolated onset of melting at about 130°C, and a peak melting point of about 131°C.

PREPARATIVE EXAMPLE C

FORM IV

- 30 Form IV was prepared by mixing Preparative Example A (550.0g, 1.54 mol) and toluene (4.0 L) and heating the mixture to 32.6°C to cause dissolution. The solution was cooled to 16.5°C and Form IV crystallized. The mixture was then cooled to 0°C over 1 hr. n-Heptane (7.0L) was added over 2 hr and the mixture was filtered. The cake was washed with 3:1 n-heptane/toluene (3.0L) and dried to give the
35 product (521.0 g) as a granular solid.

**PREPARATIVE EXAMPLE D
HEMIHYDRATE**

A solution of Preparative Example A (65 g) in 1 L of water wet toluene
5 was heated to 60°C and then cooled to ambient temperature. The hemihydrate form
crystallized and was isolated by filtration. The solids were dried at ambient
temperature under vacuum to give ~ 30 g of a colorless crystals.

**PREPARATIVE EXAMPLE E
FORM III**

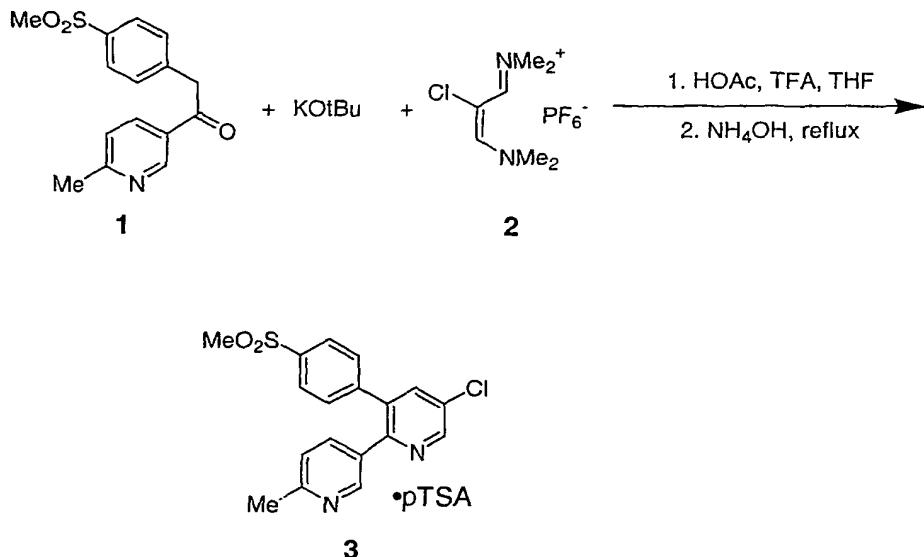
The hemihydrate of Preparative Example D was heated to 90°C in a
vacuum oven for 12 hours and cooled down in the vacuum oven to give the Form III
polymorph.

**15 PREPARATIVE EXAMPLE G
AMORPHOUS**

The amorphous form of compound A was obtained by heating the
Form IV from Preparative Example C to above its melting temperature (above about
135°C) under nitrogen, followed by quench cooling to room temperature under a dry
20 atmosphere.

**PREPARATIVE EXAMPLE H
MIXTURE OF POLYMORPHS**

Compound 1 was synthesized in accordance with Preparative Example
25 1 of U. S. Pat. No. 6,040,319. Compound 2 was synthesized in accordance with
Example 1 of U. S. Pat. No. 6,040,319.



To a slurry of Compound **1** (1.10 kg) in tetrahydrofuran (THF) (2.5 L) at 0 °C was added potassium tert-butoxide (2.47 L). The resulting mixture was transferred to a slurry of Compound **2** (1.19 kg) in THF at ambient temperature. The slurry was transferred to a solution of acetic acid (1.5 L) and trifluoroacetic acid (TFA) (0.23 L) in THF. Concentrated ammonium hydroxide (1.50 L) was added and the mixture to reflux. The reaction mixture was cooled and the phases were cut. The THF layer was concentrated and toluene was added. The toluene layer was washed with aqueous sodium hydroxide followed by water and then concentrated to ~ 6 L.

10 Acetone was added and a solution of p-toluenesulfonic acid (pTSA) (0.73 kg) in acetone was added and batch was filtered. The filter cake was washed with toluene/acetone and the solid dried in vacuo to give 1.80 kg of Compound **3** in ~ 90 % isolated yield as an off white solid.

To a mixture of toluene, water and Compound **3** (1.80 kg) was added aqueous ammonia (1 equiv.). The phases were cut and the toluene layer was washed with water. The mixture was filtered through SOLKAFLOC and the filtrate was concentrated to a saturated solution and then cooled to ambient temperature and n-heptane was added. The solid was isolated by filtration, washed with toluene/n-heptane and then dried in vacuo to give Preparative Example H as an off-white solid.

20

EXAMPLE 1

FORM V OF 5-CHLORO-3-(4-METHANESULFONYLPHENYL)-6'-METHYL-[2,3']BIPYRIDINYL

A mixture of Preparative Example H and isopropyl acetate (IPAC) was
 5 heated at 55 °C. The suspension was cooled to ambient temperature and the solids were isolated by filtration. The solids were washed with IPAC and dried in vacuo to give the Form V polymorph (1.1 kg) as a colorless solid in ~ 87 % yield.

¹H NMR (400 MHz CDCl₃) δ 8.69 (d, 1H, J=2.3 Hz), 8.36 (s, 1H, J=2.2 Hz), 7.88 (d, 2H, J=8.4 Hz), 7.72 (d, 1H, J=2.3 Hz), 7.54 (dd, 1H, J₁=8.0 Hz, J₂=2.3 Hz), 7.38 (d, 2H, J=8.5 Hz), 7.07 (d, 1H, J=8.0 Hz), 3.06 (s, 3H), 2.51 (s, 3H); ¹³C NMR (100 MHz CDCl₃) δ 158.4, 152.2, 149.7, 148.3, 143.7, 140.1, 137.9, 137.2, 135.18, 131.1, 130.0, 130.3, 127.8, 122.7, 44.4, 24.1.

CHARACTERIZATION OF POLYMORPHS

The polymorphic forms of compound A were characterized using the following procedures.

X-Ray Powder Diffraction Pattern Analysis

The X-ray patterns were collected using a Philips APD powder diffractometer utilizing copper K-alpha radiations. Table 1 below lists the XRPD peak locations for Forms I, II, III, IV and V as well as the hemihydrate and sesquihydrate forms. The peak positions are expressed in angstroms in Table 1.

25

TABLE 1

X-ray Powder Diffraction D-spacing for Crystalline Phases in Reflections (angstroms)

Form I	Form II	Form III	Form IV	Form V	Hemihydrate	Sesquihydrate
12.6	16.1	10.8	10.4	13.7	10.9	12.7
9.1	9.4	8.2	5.9	7.2	10.6	10.2
7.5	8.3	6.9	5.4	6.9	6.2	8.0
7.2	6.8	6.4	5.2	6.7	5.8	7.7
6.8	5.3	6.2	5.0	5.8	5.6	7.5
5.7	5.2	5.7	4.7	5.7	5.5	6.3
5.4	5.1	5.4	4.6	5.0	5.3	6.0
4.9	4.8	5.0	4.1	4.9	5.0	5.8
4.6	4.5	4.6	4.0	4.8	4.6	5.4

4.4	4.3	4.5	3.9	4.7	4.4	5.1
4.2	4.1	4.1	3.8	4.5	4.2	4.8
4.1	3.9	3.9	3.6	4.2	4.1	4.5
3.9	3.8	3.8	3.3	4.0	4.0	4.2
3.8	3.6	3.7	3.1	3.9	3.8	4.1
3.7	3.5	3.5	3.0	3.8	3.6	4.0
3.4	3.4	3.3		3.7	3.4	3.9
3.1	3.2	3.2		3.6	3.2	3.7
	3.0	3.1		3.4	3.1	3.5
		2.8		3.3		3.4
				3.1		3.3
				3.0		3.1
				2.9		
				2.8		

The XPRD pattern for Form V is shown in Figure 1. XRPD patterns for Forms I-IV are shown in Figures 2-5. XRPD patterns for the two hydrate forms are shown in Figures 6 and 7. The peak positions are expressed in degrees (2 theta) in
5 the plots.

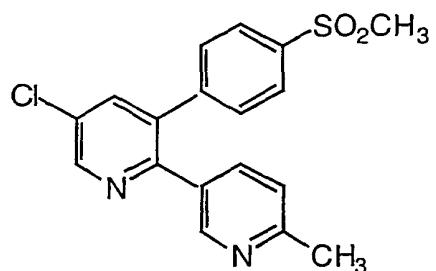
Differential Scanning Calorimetry (DSC)

DSC was carried out using a TA Instruments DSC 2910 instrument at a heating rate of 1°C/min under a nitrogen atmosphere in an open pan. The
10 extrapolated onset temperatures, T_o, and enthalpy of fusion, ΔH, observed for the melting endotherms are shown in Table 2 for Forms I, II, III, IV and V.

TABLE 2
Extrapolated melting temperature onset, T_o, and Enthalpy of Fusion obtained by DSC
15 at 1°C/min in an open pan under nitrogen

Polymorphic form	T _o (°C)	Enthalpy of fusion, J/g
Form I	135.7 ± 0.2	72.9 ± 2.0
Form II	129.6	
Form III	133.2	
Form IV	133.72 ± 0.04	76.9 ± 1.4
Form V	133.9	84.8

Another embodiment of the invention encompasses a pharmaceutical composition comprising the compound of formula A:



5

A

in combination with a pharmaceutically acceptable carrier, said compound of formula A being comprised of about 1-50% of the polymorphic form which is designated Form V and the remainder of the compound being comprised of at least one polymorphic form selected from the group consisting of: Form I, Form II, Form III and Form IV.

Another embodiment of the invention encompasses a pharmaceutical composition comprising the compound of formula A in combination with a pharmaceutically acceptable carrier, said compound of formula A being comprised of about 1-20% of the polymorphic form which is designated Form V and the remainder of the compound being comprised of at least one polymorphic form selected from the group consisting of: Form I, Form II, Form III and Form IV.

Another embodiment of the invention encompasses a pharmaceutical composition comprising the compound of formula A in combination with a pharmaceutically acceptable carrier, said compound of formula A being comprised of about 1-10% of the polymorphic form which is designated Form V and the remainder of the compound being comprised of at least one polymorphic form selected from the group consisting of: Form I, Form II, Form III and Form IV.

Within this embodiment is encompassed the pharmaceutical compositions described above wherein the polymorphic form designated Form V is characterized as having an x-ray powder diffraction pattern peak position, Cu K alpha, at about 13.7 angstroms.

Also, within this embodiment is encompassed the pharmaceutical compositions described above wherein the polymorphic form designated Form V is characterized as having at least one x-ray powder diffraction pattern peak position, Cu K alpha, at about: 7.2, 6.9, 6.7, 5.8, 5.7, 5.0, 4.9, 4.8, 4.7, 4.5, 4.2, 4.0, 3.9, 3.8, 3.7, 5. 3.6, 3.4, 3.3, 3.1, 3.0, 2.9 or 2.8 angstroms.

Also, within this embodiment is encompassed the pharmaceutical compositions described above wherein the polymorphic form designated Form V is characterized as having a DSC extrapolated onset melting temperature of about 133.9°C.

10 Also within this embodiment is encompassed the pharmaceutical compositions described above wherein the polymorphic form designated Form V is characterized as having a DSC peak melting temperature of about 134.5°C.

15 The invention also encompasses a method of treating an inflammatory disease susceptible to treatment with an non-steroidal anti-inflammatory agent comprising administering to a patient in need of such treatment a therapeutically effective amount of the pharmaceutical compositions described above.

20 The invention also encompasses a method of treating a cyclooxygenase mediated disease advantageously treated by an active agent that selectively inhibits cyclooxygenase-2 in preference to cyclooxygenase-1 comprising administering to a patient in need of such treatment a therapeutically effective amount of the pharmaceutical compositions described above.

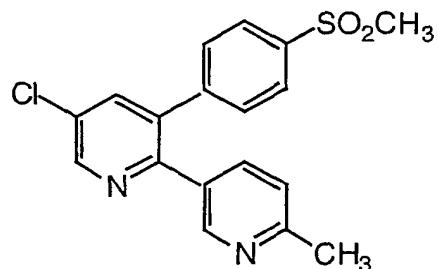
25 The invention also encompasses a method for treating an illness selected from the group consisting of: (a) rheumatic fever, (b) symptoms associated with influenza or other viral infections, common cold, (c) low back and neck pain, (d) dysmenorrhea, (e) headache, (f) toothache, (g) sprains and strains, (h) myositis, (i) neuralgia, (j) synovitis, (k) arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, (l) bursitis, (m) burns, (n) injuries, and (o) following surgical and dental procedures, comprising administering to a patient in need of such treatment a therapeutically effective amount of the 30 pharmaceutical compositions described above.

35 Polymorphic forms I, II, III and IV as well as the hemihydrate, sesquihydrate and amorphous forms of the compound of Formula A are described in WO/0137833 published on May 31, 2001, which is hereby incorporated by reference in its entirety.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising the compound of formula A:

5



A

in combination with a pharmaceutically acceptable carrier,

10

said compound of formula A being comprised of about 1-50% of the polymorphic form which is designated Form V and the remainder of the compound being comprised of at least one polymorphic form selected from the group consisting of: Form I, Form II, Form III and Form IV.

15

2. The pharmaceutical composition according to Claim 1 wherein:

20 said compound of formula A is comprised of about 1-20% of the polymorphic form which is designated Form V and the remainder of the compound being comprised of at least one polymorphic form selected from the group consisting of: Form I, Form II, Form III and Form IV.

3. The pharmaceutical composition according to Claim 2 wherein:

25 said compound of formula A is comprised of about 1-10% of the polymorphic form which is designated Form V and the remainder of the compound being comprised of

at least one polymorphic form selected from the group consisting of: Form I, Form II, Form III and Form IV.

4. The pharmaceutical composition according to Claim 1 wherein
5 the polymorphic form designated Form V is characterized as having an x-ray powder
diffraction pattern peak position, Cu K alpha, at about 13.7 angstroms.

5. The pharmaceutical composition according to Claim 1 wherein
the polymorphic form designated Form V is characterized as having at least one x-ray
10 powder diffraction pattern peak position, Cu K alpha, at about: 7.2, 6.9, 6.7, 5.8, 5.7,
5.0, 4.9, 4.8, 4.7, 4.5, 4.2, 4.0, 3.9, 3.8, 3.7, 3.6, 3.4, 3.3, 3.1, 3.0, 2.9 or 2.8
angstroms.

6. The pharmaceutical composition according to Claim 1 wherein
15 the polymorphic form designated Form V is characterized as having a DSC
extrapolated onset melting temperature of about 133.9°C.

7. The pharmaceutical composition according to Claim 1 wherein
the polymorphic form designated Form V is characterized as having a DSC peak
20 melting temperature of about 134.5°C.

8. A method of treating an inflammatory disease susceptible to
treatment with a non-steroidal anti-inflammatory agent comprising administering to
a patient in need of such treatment a therapeutically effective amount of the
25 pharmaceutical composition according to Claim 1.

9. A method of treating a cyclooxygenase mediated disease
advantageously treated by an active agent that selectively inhibits cyclooxygenase-2 in
preference to cyclooxygenase-1 comprising administering to a patient in need of such
30 treatment a therapeutically effective amount of the pharmaceutical composition
according to Claim 1.

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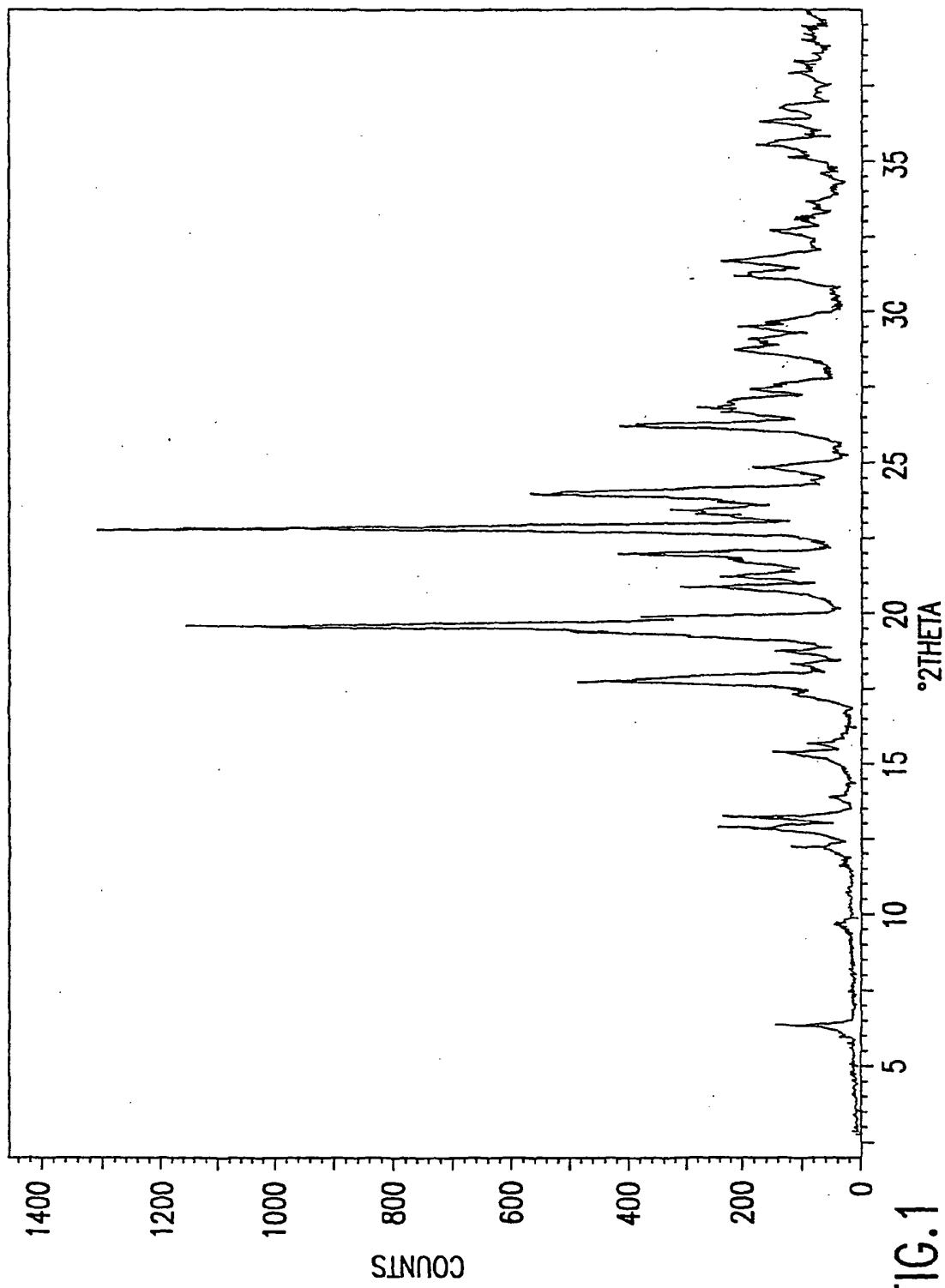


FIG. 1

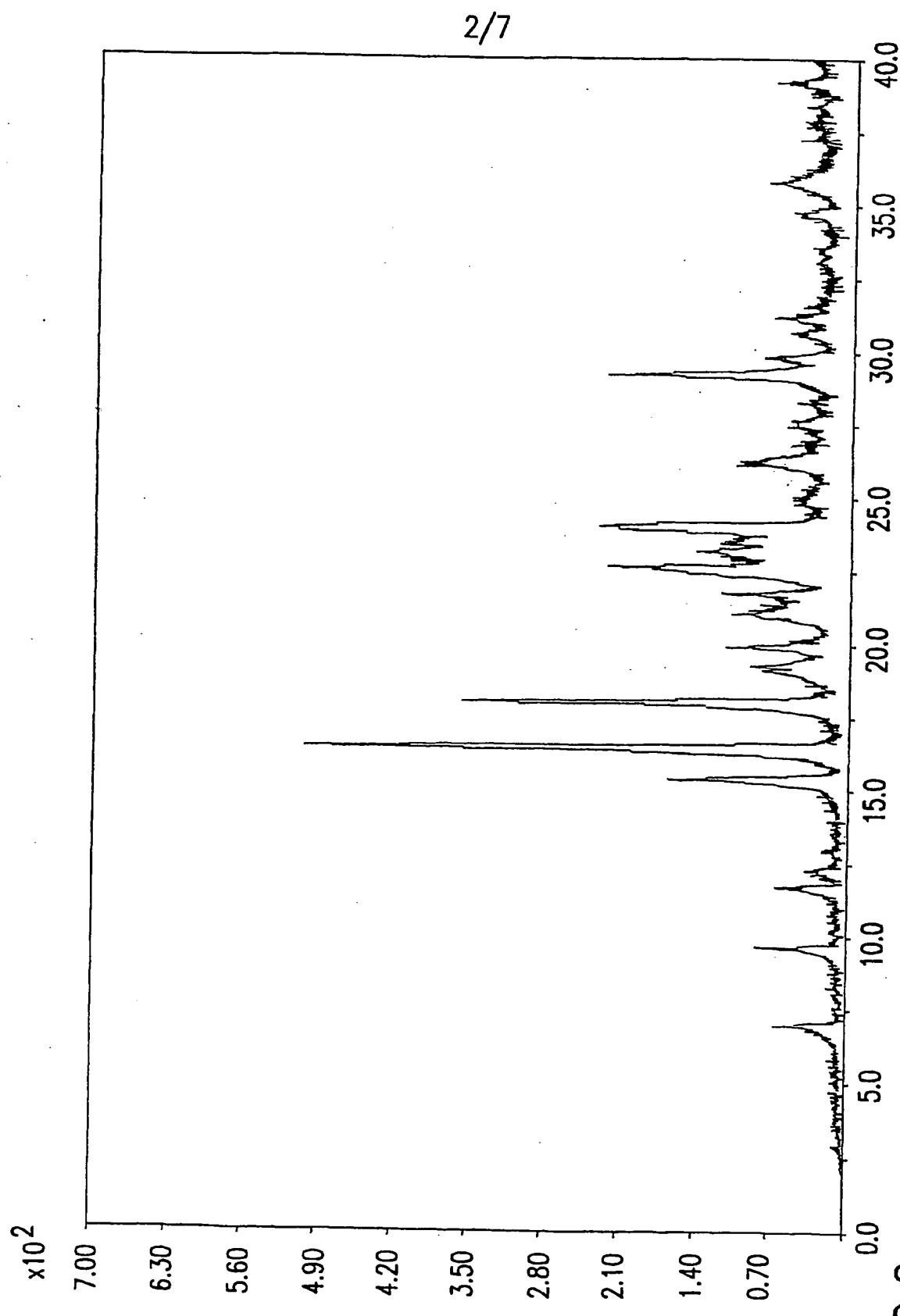


FIG. 2

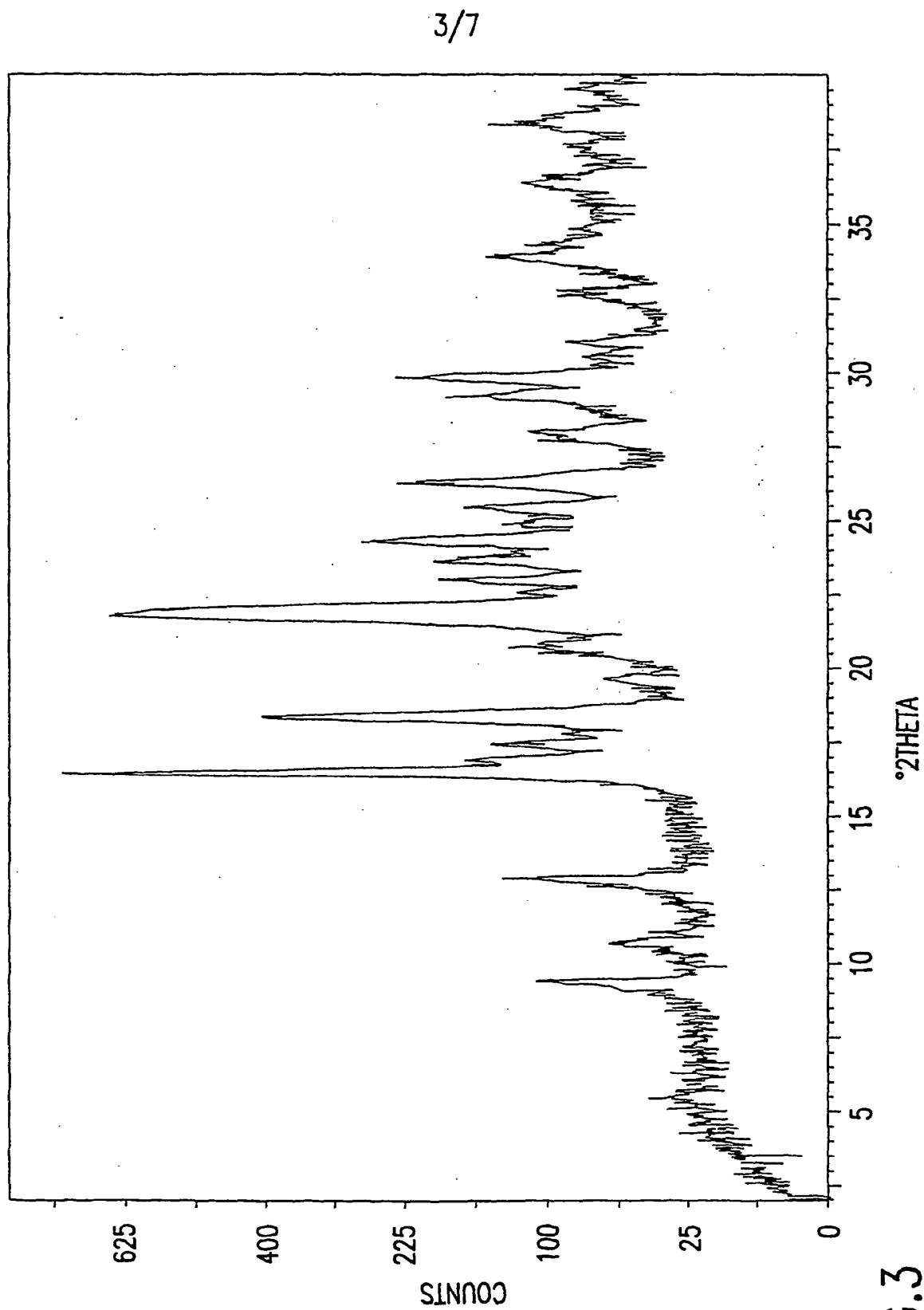


FIG. 3

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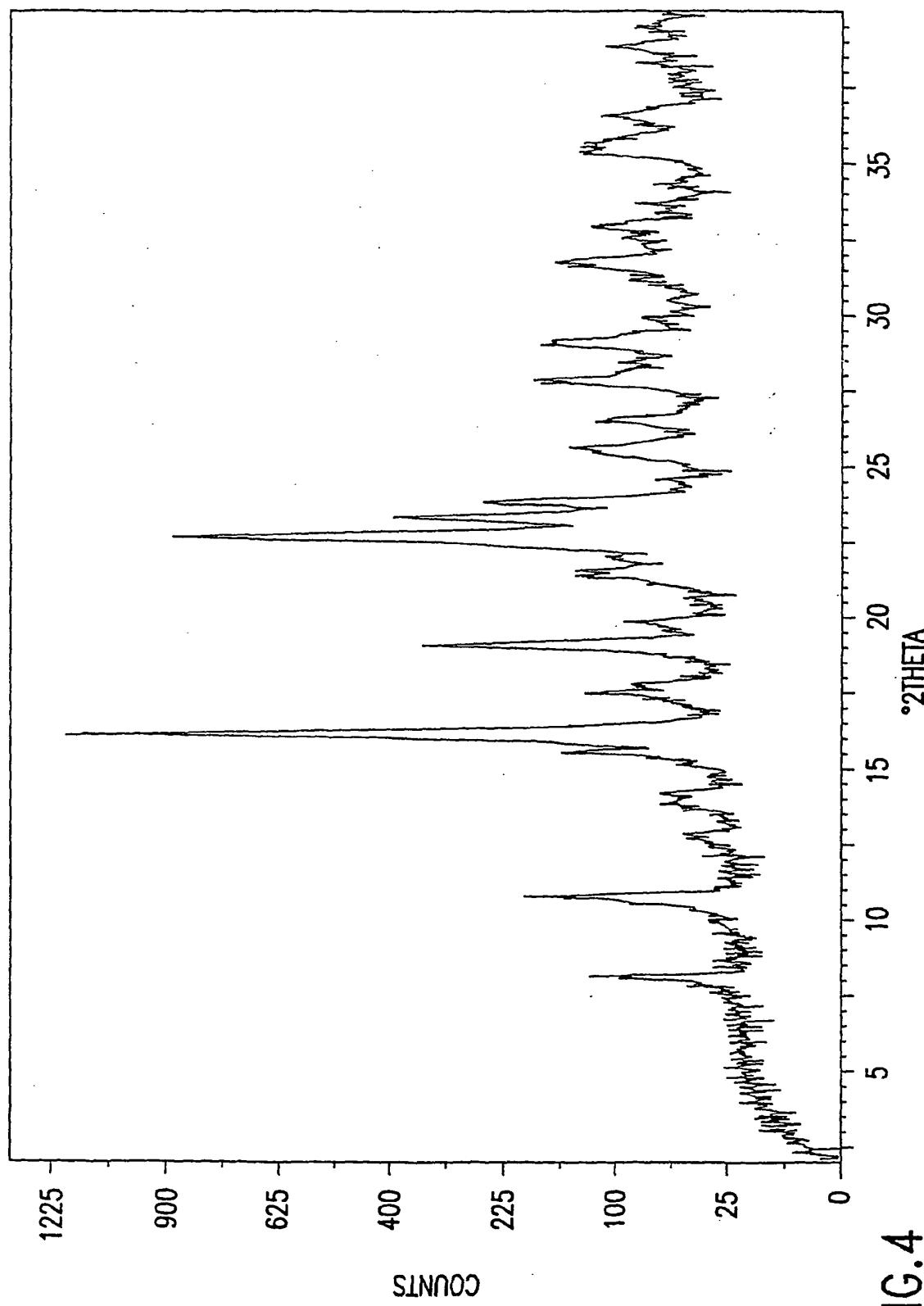
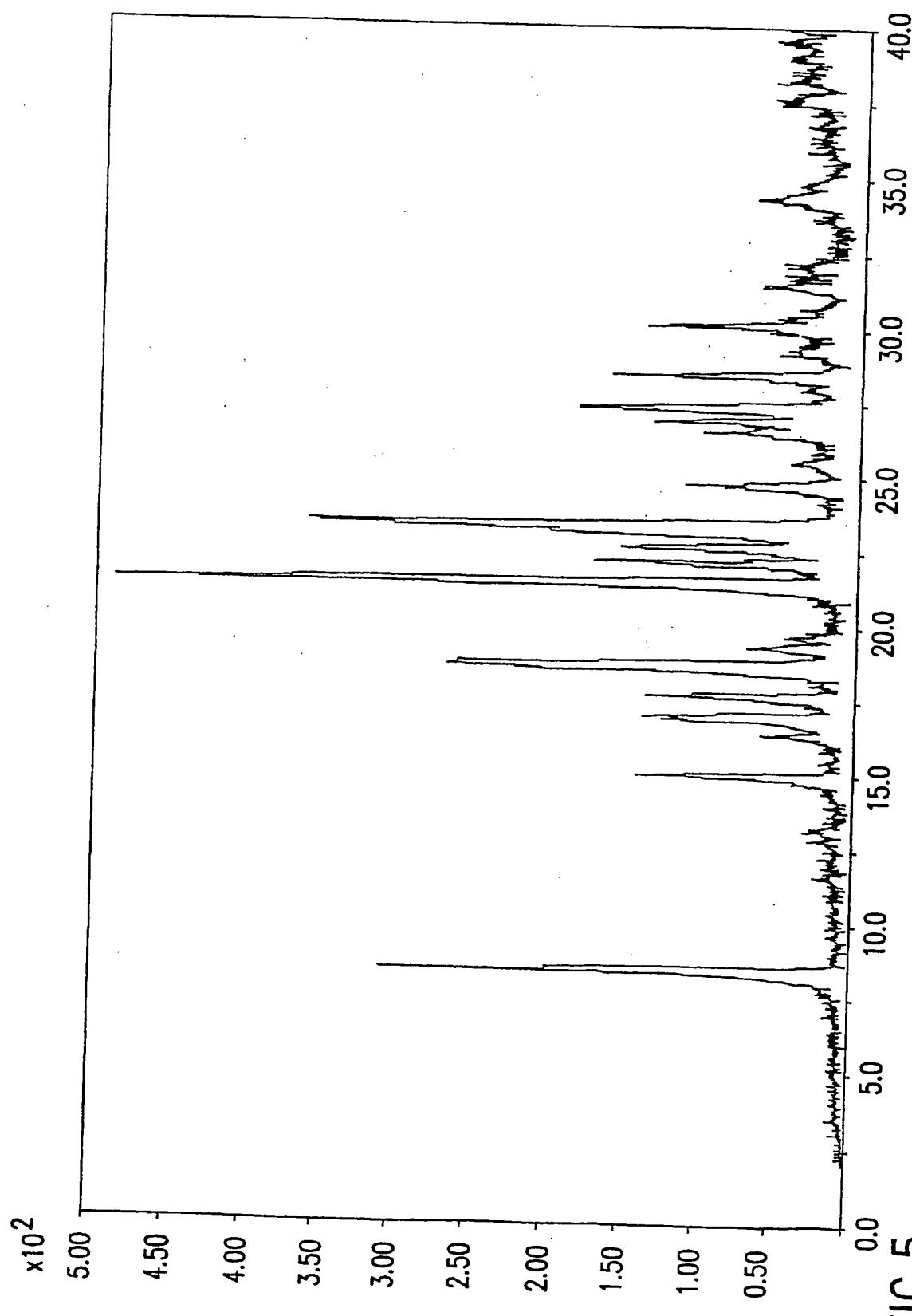


FIG. 4

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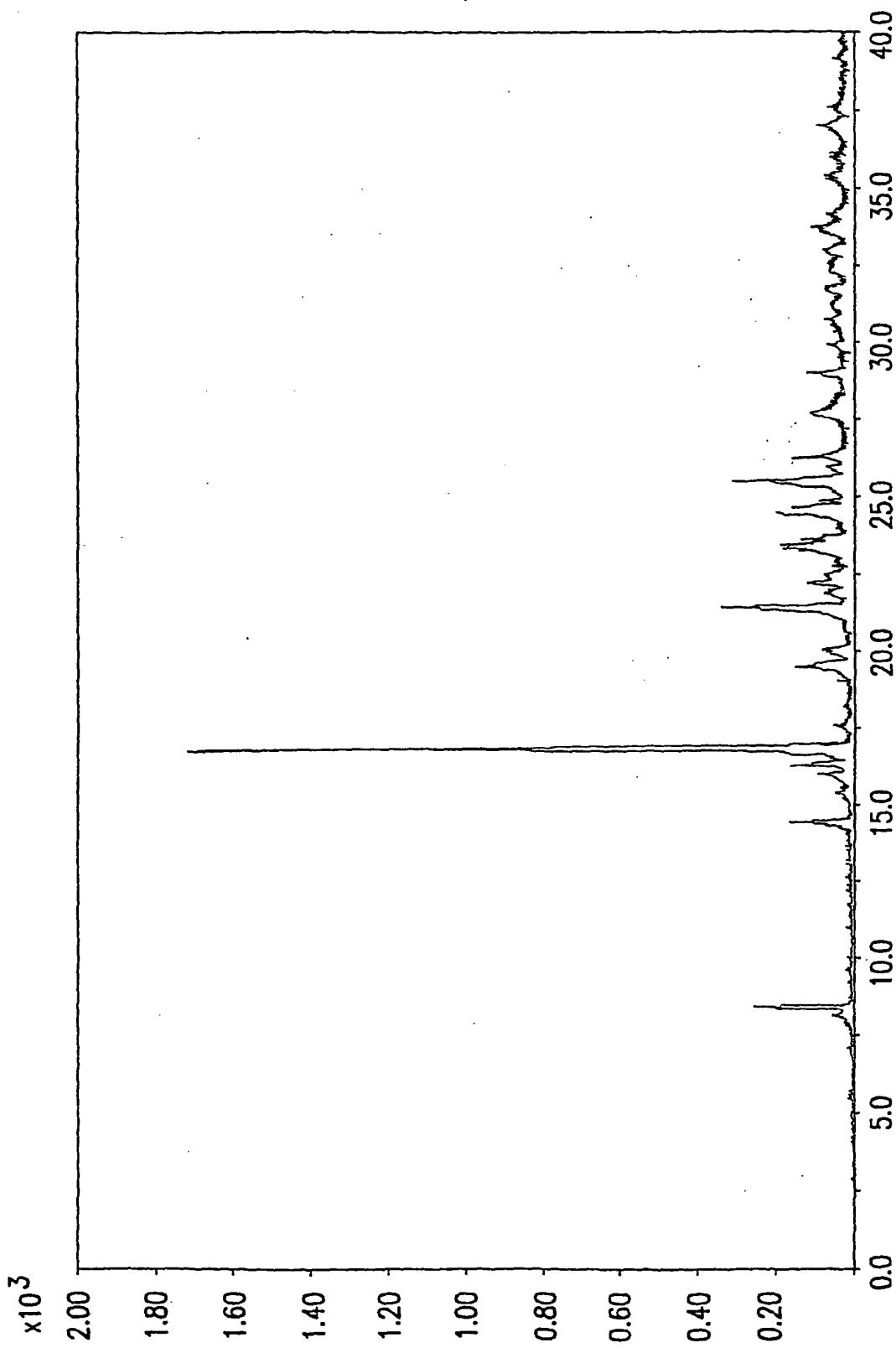


FIG. 6

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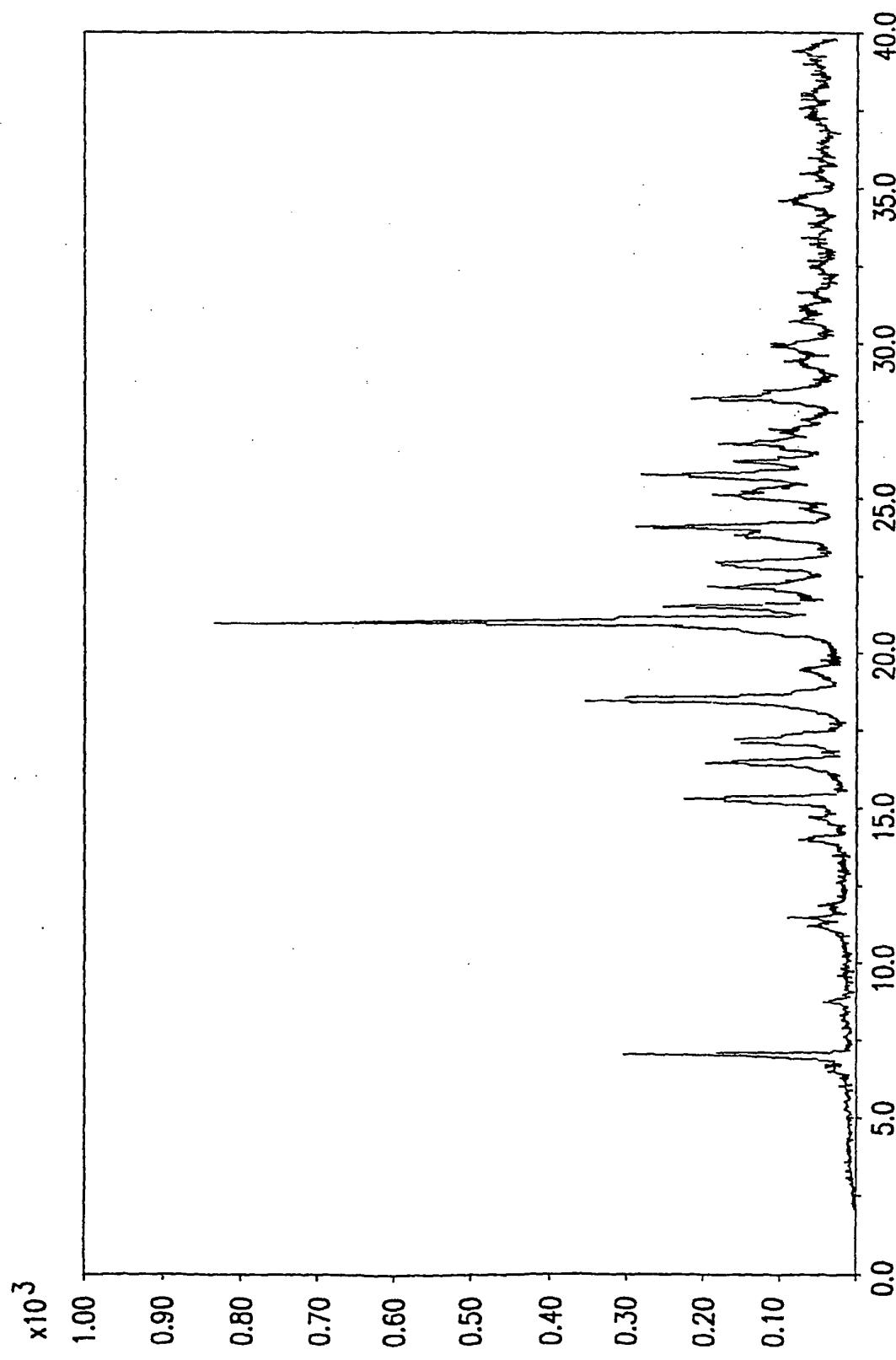


FIG. 7

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/29551

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C07D 213/62;A61K31/44

US CL : 546/261;514/884

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/261;514/884

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, EAST

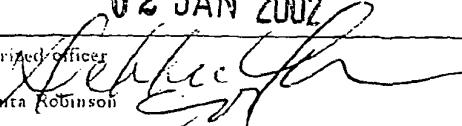
C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Davies, J. M. A Practical Synthesis of a COX-2-Specific Inhibitor. 2000. 65. No. 25.	1-9

Further documents are listed in the continuation of Box C. See patent family annex.

Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance: the claimed invention cannot be considered novel or can only be considered to involve an inventive step when the document is taken alone
"B" earlier document published on or after the international filing date	"Y"	document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claims(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Z"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
20 NOVEMBER 2001	02 JAN 2002

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized Officer 
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